Serial No.: 09/412,284 Filing Date: 10/05/99
Applicants: Allaway, G., *et al.* Priority Date: 03/16/98-CON
06/07/95-CIP

Search Strategy

FILE 'USPATFULL' ENTERED AT 14:59:08 ON 11 DEC 2000

		E	ALLAWAY G P/IN
L1	4	S	E4
		E	LITWIN VIRGINIA M/IN
L2	2	S	E3
		E	MADDON PAUL J/IN
L3	12	S	E3
L4	11385	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L5	3619	S	L4 AND FUSION
L6	3221	S	L5 AND INHIBIT?
L7	1190	S	L4 AND SYNCYTIA?
L8	1067	S	L7 AND INHIBIT?
L9	3645	S	L6 OR L8
L10	650	S	(INHIBIT? (5W) FUSION OR INHIBIT? (5W) SYNCYTIA?)
L11	503	S	L10 AND (ANTIBOD?)
L12	10	S	L11 AND (MACROPHAGE-TROPIC OR MONOCYTE-TROPIC)
L13	27	S	L11 AND (PRIMARY ISOLATE?)
L14	24	S	L13 NOT L12

FILE 'WPIDS' ENTERED AT 15:16:39 ON 11 DEC 2000

		E	ALLAWAY G P/IN
L15	12	S	E3
		E	LITWIN V M/IN
L16	8	S	E3
		E	MADDON P J/IN
L17	22	S	E3
L18	8019	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L19	355	S	L18 AND FUSION
L20	177	S	L19 AND INHIBIT?
L21	101	S	L20 AND ANTIBOD?
L22	1	S	L21 AND (MACROPHAGE-TROPIC OR MONOCYTE-TROPIC)
L23	3	S	L21 AND (PRIMARY ISOLATE?)

FILE 'AIDSLINE' ENTERED AT 15:22:44 ON 11 DEC 2000

		E	ALLAWAY G/AU
L24	19	S	E4
		E	LITWIN V M/AU
L25	3	S	E2
		E	MADDON P J/AU
L26	36	S	E3
L27	138207	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L28	3141	S	L27 AND FUSION
L29	1049	S	L27 AND SYNCYTIA?
L30	3910	S	L29 OR L28
L31	1553	S	L30 AND INHIBIT?
L32	552	S	L31 AND ANTIBOD?
L33	23	S	L32 AND (MACROPHAGE-TROPIC OR MONOCYTE-TROPIC)
L34	12	S	L32 AND (PRIMARY ISOLATE?)
L35	9	S	L34 NOT L33
L36	520	S	L32 NOT (L33 OR L34)
L37	194	S	L36 AND NEUTRALIZ?

L1 ANSWER 1 OF 4 USPATFULL
2000:109525 Method for preventing HIV-1 infection of CD4.sup.+ cells.
Allaway, Graham P. , Mohegan Lake, NY, United States
Litwin, Virginia M., Fayetteville, NY, United States
Maddon, Paul J., Elmsford, NY, United States
Olson, William C., Ossining, NY, United States
Progenics Pharmaceuticals, Inc., Tarrytown, NY, United States (U.S. corporation)
US 6107019 20000822
APPLICATION: US 1997-876078 19970613 (8)
PRIORITY: US 1996-19715 19960614 (60)
US 1996-14532 19960402 (60)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides methods for inhibiting fusion of HIV-1 to CD4.sup.+ cells which comprise contacting CD4.sup.+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4.sup.+ cells is inhibited. This invention also provides methods for inhibiting HIV-1 infection of CD4.sup.+ cells which comprise contacting CD4.sup.+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4.sup.+ cells is inhibited, thereby inhibiting the HIV-1 infection. This invention provides non-chemokine agents capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4.sup.+ cells. This invention also provides pharmaceutical compositions comprising an amount of the non-chemokine agent capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4.sup.+ cells effective to prevent fusion of HIV-1 to CD4.sup.+ cells and a pharmaceutically acceptable carrier.

CLM What is claimed is:
1. An in vitro method for determining whether an agent is capable of inhibiting HIV-1 infection of a CD4.sup.+ cell susceptible to HIV-1 infection comprising the steps of: (a) fixing a chemokine receptor on a solid matrix wherein the chemokine receptor is a co-receptor for HIV-1 infection; (b) contacting the fixed chemokine receptor with the agent under conditions permitting binding of the agent to the chemokine receptor; (c) removing any unbound agent; (d) contacting the resulting fixed chemokine receptor to which the agent is bound with a predetermined amount of gp120/CD4.sup.+ complex under conditions permitting binding of gp120/CD4 .sup.+ complex to the fixed chemokine receptor in the absence of the agent; (e) removing any unbound gp120/CD4.sup.+ complex; (f) measuring the amount of gp120/CD4.sup.+ complex bound to the fixed chemokine receptor; and (g) comparing the amount measured in step (f) with the amount measured in the absence of the agent, a decrease in the amount bound in the presence of the agent indicating that the agent is capable of inhibiting HIV-1 infection.

2. An in vitro method for determining whether an agent is capable of inhibuting HIV-1 infection of a CD4.sup.+ cell susceptible to HIV-1 infection comprising the steps: (a) fixing a chernokine receptor on a solid matrix wherein the chemokine receptor is a co-receptor for HIV-1 infection; (b) contacting the fixed chemokine receptor with the agent and a predetermined amount of gp120/CD4.sup.+ complex under conditions permitting binding of the gp120/CD4.sup.+ complex to the fixed chemokine receptor in the absence of the agent; (c) removing any unbound agent or unbound gp120/CD4.sup.+ complex or both; (d) measuring the amount of gp120/CD4.sup.+ complex bound to the fixed chemokine receptor; and (e) comparing the amount measured in step (d) with the

amount measured in the absence of the agent, a decrease in the amount bound in the presence of the agent indicating that the agent is capable of inhibiting HIV-1 infection.

3. An in vitro method for determining whether an agent is capable of inhibiting HIV-1 infection of a CD4.sup.+ cell susceptible to HIV-1 infection comprising steps of: (a) fixing a gp120/CD4.sup.+ complex on a solid matrix; (b) contacting the fixed gp120/CD4.sup.+ complex with the agent under conditions permitting the binding of the agent to the gp120/CD4.sup.+ complex; (c) removing any unbound agent; (d) contacting the resulting fixed gp120/CD4.sup.+ complex to which the agent is bcund with a predetermined amount of chemokine receptor, wherein the chemokine receptor is a co-receptor for HIV-1 infection, under conditions permitting binding of the chemokine receptor to the fixed the gp120/CD4.sup.+ complex in the absence of the agent; (e) removing any unbound chemokine receptor; (f) measuring the amount of chemokine receptor bound to the fixed gp120/CD4.sup.+ ; and (g) comparing the amount measured in step (f) with the amount measured in the absence of the agent, a decrease in the amount bound in the presence of the agent indicating that the agent is capable of inhibiting HIV-1 infection.

4. An in vitro method for determining whether an agent is capable of inhibiting HIV-1 infection of a CD4.sup.+ cell susceptible to HIV-1 infection comprising steps of: (a) fixing a gp120/CD4.sup.+ complex on a solid matrix: (b) contacting the fixed gp120/CD4.sup.+ complex with the agent and a predetermined amount of chemokine receptor, wherein the chemokine receptor is a co-receptor for HIV-1 infection, under co)nditions permitting binding of the chemokine receptor to the fixed gp120/CD4.sup.+ complex in the absence of the agent; (c) removing any unbound agent or any unbound chemokine receptor or both: (d) measuring the amount of chemorkine receptor bound to the fixed gp120/CD4.sup.+ ; and (e) comparing the amount measured in step (d) with the amount measured in the absence of the agent, a decrease in the amount bound in the presence of the agent indicating that the agent is capable of inhibiting HIV-1 infection.

5. The method of claim 1, 2, 3, or 4 wherein the CD4.sup.+ is a soluble CD4.sup.+.

6. The method of claim 1, 2, 3, or 4 wherein the chemokine receptor is expressed on a cell.

7. The method of claim 6 wherein the cell is a L1.2 cell.

8. The method of claim 1 or 2, wherein the gp120, CD4.sup.+ or both are labeled with a detectable marker.

9. The method of claim 3 or 4 wherein the chemokine receptor is labeled with a detectable marker.

10. The method of claim 1 or 2, wherein the gp120, CD4.sup.+ or both are labeled with biotin.

11. The method of claim 2 or 4 wherein the chemokine receptor is labeled with biotin.

12. The method of any one of claims 1, 2, 3, or 4, wherein the chemockine receptor is CCR5.

L12 ANSWER 2 OF 10 USPATFULL
1999:155898 ***Antibodies*** directed against cellular coreceptors for

human immunodeficiency virus and methods of using the same.
Hoxie, James A., Berwyn, PA, United States
Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)
US 5994515 19991130
APPLICATION: US 1997-882435 19970625 (8)
PRIORITY: US 1996-20396 19960627 (60)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to an anti-immunodeficiency virus ***antibody*** which binds to a cellular protein and diagnostic and therapuetic methods of using the same.

L12 ANSWER 4 OF 10 USPATFULL
1999:120880 ***Antibodies*** against a host cell antigen complex for pre- and post-exposure protection from infection by HIV.
Wang, Chang Yi, Cold Spring Harbor, NY, United States
United Biomedical, Inc., Hauppauge, NY, United States (U.S. corporation)
US 5961976 19991005
APPLICATION: US 1997-808374 19970228 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention is directed to monoclonal ***antibodies*** produced by using CD4-expressing T lymphocytes, such as peripheral blood mononuclear T cells, thymocytes, splenocytes and leukemia or lymphoma derived T cell line cells such as HPB-ALL or SUP-T as the immunogen in accordance with the protocols and screening procedures described. The monoclonal ***antibodies*** of the present invention are characterized by their ability to neutralize in vitro and in vivo primary isolates of Human Immunodeficiency Virus (HIV) and related immunodeficiency viruses. The ***antibodies*** are directed against a host cell antigen complex comprising CD4 protein in association with domains from chemokine receptors and have broad neutralizing activities against primary isolates from all clades of HIV type 1 (HIV-1) and primary isolates of HIV type 2 (HIV-2) and Simian Immunodeficiency Virus (SIV). The present invention is also directed to a method of selecting and producing such ***antibodies*** , hybridomas which secrete such ***antibodies*** , pharmaceutical compositions comprising such ***antibodies*** and methods for pre- and post-exposure prevention of immunodeficiency virus infection in primates, including humans, by such ***antibodies*** whose primary targets are CD4 expressing lymphocytes.

L12 ANSWER 7 OF 10 USPATFULL
1999:67195 ***Antibodies*** against a host cell antigen complex for pre and post exposure protection from infection by HIV.
Wang, Chang Yi, Cold Spring Harbor, NY, United States
United Biomedical, Inc., Hauppuage, NY, United States (U.S. corporation)
US 5912176 19990615
APPLICATION: US 1997-867149 19970602 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention is directed to monoclonal ***antibodies*** produced by using CD4-expressing T lymphocytes, such as peripheral blood mononuclear T cells, thymocytes, splenocytes and leukemia or lymphoma derived T cell line cells such as HPB-ALL or SUP-T as the immunogen in accordance with the protocols and screening procedures described. The monoclonal ***antibodies*** of the present invention are characterized by their ability to neutralize in vitro and in vivo primary isolates of Human Immunodeficiency Virus (HIV) and related immunodeficiency viruses. The ***antibodies*** are directed against

a host cell antigen complex comprising CD4 protein in association with domains from chemokine receptors and have broad neutralizing activities against primary isolates from all clades of HIV type 1 (HIV-1) and primary isolates of HIV type 2 (HIV-2) and Simian Immunodeficiency Virus (SIV). The present invention is also directed to a method of selecting and producing such ***antibodies*** , hybridomas which secrete such ***antibodies*** , pharmaceutical compositions comprising such ***antibodies*** and methods for pre- and post-exposure prevention of immunodeficiency virus infection in primates, including humans, by such ***antibodies*** whose primary targets are CD4 expressing lymphocytes.

L14 ANSWER 7 OF 24 USPATFULL
2000:24446 Neutralizing ***antibodies*** against HIV infection.
Devico, Anthony L., Alexandria, VA, United States
Pal, Ranajit, Gaithersburg, MD, United States
Sarngadharan, Mangalasseril G., McLean, VA, United States
Akzo Nobel N.V., Arnhem, Netherlands (non-U.S. corporation)
US 6030772 20000229
APPLICATION: US 1998-75544 19980511 (9)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Neutralizing ***antibodies*** against HIV infection are provided. The ***antibodies*** are reactive with cryptic epitopes on gp120 and/or CD4 induced by the formation of immunogenic complexes comprising gp120 covalently bonded to CD4 or to succinyl concanvalin A.

L14 ANSWER 16 OF 24 USPATFULL
1998:108273 Human neutralizing monoclonal ***antibodies*** to human immunodeficiency virus.
Burton, Dennis R., La Jolla, CA, United States
Barbas, Carlos F., San Diego, CA, United States
Lerner, Richard A., La Jolla, CA, United States
The Scripps Research Institute, La Jolla, CA, United States (U.S. corporation)
US 5804440 19980908
APPLICATION: US 1997-899575 19970724 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention describes human monoclonal ***antibodies*** which immunoreact with and neutralize human immunodeficiency virus (HIV). Also disclosed are immunotherapeutic and diagnostic methods of using the monoclonal ***antibodies*** , as well as cell line for producing the monoclonal ***antibodies*** .

L14 ANSWER 20 OF 24 USPATFULL
97:94275 Compound for inhibiting HIV infectivity.
Singh, Shyam K., Natick, MA, United States
Patch, Raymond J., Framingham, MA, United States
Pallai, Peter V., Westwood, MA, United States
Neidhardt, Edith A., Boxford, MA, United States
Palace, Gerard P., Framingham, MA, United States
Willis, Kevin J., Newton, MA, United States
Sampo, Theresa M., Watertown, MA, United States
McDonald, Kevin W., Merrimack, NH, United States
Shi, Zhan, Waltham, MA, United States
Procept, Inc., Cambridge, MA, United States (U.S. corporation)
US 5677343 19971014
APPLICATION: US 1995-467725 19950606 (8)
DOCUMENT TYPE: Utility.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention pertains to the discovery that condensation polymers of an aldehyde and aromatic sulfonic acids and fractions thereof, such as formaldehyde naphthalene-sulfonic acid condensation polymers, can abrogate HIV gp120 binding to CD4, as demonstrated in CD4/gp120 binding assays. In addition to gp120 binding inhibition, the compounds have been shown to ***inhibit*** HIV-induced ***syncytia*** formation and infectivity of CD+ cells. The use of this compound has been shown to be non-cytotoxic and non-inhibitory to antigen induced T lymphocyte proliferation. Based on these findings, these compounds can be used as a therapeutic agent for the treatment of acquired immunodeficiency syndrome (AIDS), as well as AIDS-related complex (ARC), AIDS-related dementia and non-symptomatic HIV infection. The compounds can also be used to treat blood preparations.

L14 ANSWER 21 OF 24 USPATFULL
97:66028 Human neutralizing monoclonal ***antibodies*** to human immunodeficiency virus.
Burton, Dennis R., La Jolla, CA, United States
Barbas, Carlos F., San Diego, CA, United States
Lerner, Richard A., La Jolla, CA, United States
The Scripps Research Institute, La Jolla, CA, United States (U.S. corporation)
US 5652138 19970729
APPLICATION: US 1994-276852 19940718 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention describes human monoclonal ***antibodies*** which immunoreact with and neutralize human immunodeficiency virus (HIV). Also disclosed are immunotherapeutic and diagnostic methods of using the monoclonal ***antibodies*** , as well as cell line for producing the monoclonal ***antibodies*** .

L23 ANSWER 1 OF 3 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 2000-431480 [37] WPIDS
DNC C2000-131148
TI Preventing and treating ***human*** ***immunodeficiency*** ***virus*** (***HIV***) infections using compounds that ***inhibit*** interactions between ***HIV*** and its ***fusion*** co-receptor, especially ***antibodies*** specific for the CCR5 chemokine receptor.
DC B04 D16
IN MADDON, P J; OLSON, W C
PA (PROG-N) PROGENICS PHARM INC
CYC 22
PI WO 2000035409 A2 20000622 (200037)* EN 68p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP MX
AU 2000021996 A 20000703 (200046)
ADT WO 2000035409 A2 WO 1999-US30345 19991216; AU 2000021996 A AU 2000-21996 19991216
FDT AU 2000021996 A Based on WO 200035409
PRAI US 1998-212793 19981216; US 1998-112532 19981216

AB WO 200035409 A UPAB: 20000807
NOVELTY - A composition (I) for ***inhibiting*** ***human*** ***immunodeficiency*** ***virus*** (***HIV***)-1 infection, comprising at least 2 synergistic compounds (especially ***antibodies*** specific for chemokine receptor CCR5) for ***inhibiting*** ***HIV*** infection, is new. At least 1 of the compounds prevents productive interaction between ***HIV*** -1 and a ***HIV*** -1 ***fusion*** co-receptor.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a method (II) for treating a subject infected with ***HIV*** -1, or preventing a subject becoming infected, comprising administering (I);
(2) an anti-CCR5 monoclonal ***antibody*** (III), selected from PA8 (ATCC HB-12605), PA9 (ATCC HB-12606), PA10 (ATCC HB-12607), PA11 (ATCC HB-12608), PA12 (ATCC HB-12609) and/or PA14 (ATCC HB-12610);
(3) a nucleic acid molecule (IV) encoding the light chain from (III);
(4) a nucleic acid molecule (V) encoding the heavy chain from (III);
(5) a nucleic acid molecule (VI) encoding the Fab chain from (III);
(6) a nucleic acid molecule (VII) encoding the CDR (complementary determining region) from (VIII); and
(7) nucleic acid molecules (IX) encoding the variable region from (III).
ACTIVITY - Viricidal.
MECHANISM OF ACTION - ***Inhibition*** of interactions between ***HIV*** -1 and ***HIV*** -1 ***fusion*** co-receptors, especially ***antibody*** ***inhibition*** of CCR5 chemokine receptor binding.
HIV -1 envelope-mediated ***fusion*** between HeLa-EnvJR-FL+ and PM1 cells was detected using the RET (resonance energy transfer) assay. Equal numbers (2 multiply 104) of fluorescein octadecyl ester (F18)-labeled envelope expressing cells and octadecyl rhodamine (R18)-labeled PM1 cells were plated in 96-well plates in 15% fetal calf serum in DPBS (undefined) and incubated for 4 hours (h) at 37 deg. C in the presence of varying concentrations of the anti-CCR5 mAbs (monoclonal ***antibodies***), PA8 to PA12, PA14, 2D7 or a non-specific murine IgG1. Fluorescence RET was measured with a Cytofluor (RTM) plate-reader and % RET was determined as described by Litwin V et al., ***HIV*** -1 membrane ***fusion*** mediated by laboratory adapted strain and a ***primary*** ***isolate*** analyzed by resonance energy transfer,

J. Virol., 70:6437-6441.

NLluc+env- viruses complemented in trans by envelope glycoproteins from JR-FL or Gun-1 were produced as previously described by Dragic TV et al., Amino terminal substitutions in the CCR5 co-receptor impair gp120 binding and ***HIV*** -1 entry, J. Virol., 72:279-285. U87MG-CD4+CCR5+ cells were infected with chimeric, reporter viruses containing 50-100 ng/ml p24 in the presence of varying concentrations of the individual mAbs. After 2h at 37 deg. C, virus-containing media were replaced by fresh, mAb-containing media. Fresh media, without ***antibodies*** , was added again after 12 h. After a total of 72h, 100 microliters of lysis buffer were added to the cells and luciferase activity (r.l.u.) was measured as described by Dragic et al., supra. The percentage ***inhibition*** of ***HIV*** -1 infection was defined as (1-(r.l.u in the presence of ***antibody*** / r.l.u in the absence of ***antibody***)) x 100%.

All 6 mAbs and mAb 2D7 blocked ***fusion*** between CD4+CCR5+ PM1 cells and HeLa-EnvJR-FL+ cells in the RET assay. The descending rank order of potency was 2D7, PA14, PA12, PA11, PA10, PA9, PA8. The IC50 values for PA14 and 2D7 were 1.7 micrograms/ml and 1.6 micrograms/ml (respectively), for PA11 and PA12 is was 25.5 micrograms/ml and 10 micrograms/ml (respectively). PA8, PA9 and PA10 ***inhibited*** ***fusion*** by 10-15% at 300 micrograms/ml. None of the mAbs affected ***fusion*** between PM1 cells and HeLa-EnvLai+ cells which express the full length envelope protein from an X4 virus.

USE - (I) is used for preventing and treating infections caused by ***HIV*** -1 viruses (e.g. acquired immunodeficiency syndrome (AIDS)).

Dwg.0/6

L23 ANSWER 2 OF 3 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 2000-205667 [18] WPIDS
DNC C2000-063447
TI New ***fusion*** related molecular structure useful for preventing and treating viral diseases, e.g. ***HIV*** infection in a human fetus.
DC B04 C06 D16
IN NUNBERG, J H
PA (UYMO-N) UNIV MONTANA
CYC 86
PI WO 2000008043 A2 20000217 (200018)* EN 118p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9957715 A 20000228 (200030)
ADT WO 2000008043 A2 WO 1999-US17487 19990803; AU 9957715 A AU 1999-57715 19990803
FDT AU 9957715 A Based on WO 200008043
PRAI US 1999-141806 19990629; US 1998-95105 19980803

AB WO 200008043 A UPAB: 20000412
NOVELTY - New isolated molecular structure (I) comprises an epitope formed by the ***fusion*** of a virus envelope protein (or mutant) (II), with one or more cellular membrane proteins (III) at low pH.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a recombinant enveloped virus expressing on the envelope a cell receptor for a native envelope protein;

(2) a monoclonal ***antibody*** (IV) to (I);

(3) purified polyclonal antiserum (V) specific to (I);

(4) a contraceptive jelly, foam, cream or ointment comprising (IV) or

(V) for ***inhibiting*** or decreasing the viral infection;
(5) a cell line (cl) recombinantly expressing (II);
(6) monitoring the production of (IV) in a subject comprising isolating a sample containing serum and detecting (IV);
(7) preparing an immunogen (Ia) for use in a vaccine;
(8) (Ia) obtained in the form of a cross-linked structure;
(9) screening (I) for vaccine efficacy comprising immunizing a transgenic non-human mammal (which expresses one or more transgenes, both human CD4 and a co-receptor for ***HIV***) with (I) and detecting ***antibodies*** to ***HIV*** ;
(10) an isolated protein complex (VI) comprising (II) of ***HIV*** type I functionally interacting with human CD4 and CCR5;
(11) a vaccine formulation (VII) comprising (I) or nucleic acid encoding (II) and (III)/(VI);
(12) preparation of (VI);
(13) fixed cells prepared from (12);
(14) purifying (VI) comprising tagging (VI) with a peptide sequence and isolating the tagged complex;
(15) a composition comprising (IV) and (II), and
(16) a kit comprising labeled (IV), (I), or nucleic acid encoding (II) and (III).
ACTIVITY - Antiviral; anti- ***HIV*** .
MECHANISM OF ACTION - Vaccine; gene therapy. No supporting data is given.
USE - (I) and (IV) are useful for treating and preventing viral infection in humans and domestic animals preferably ***HIV*** infection in a human fetus. (VII) is useful for immunizing animals against viral infection. (IV) is also useful for decontaminating surgical and dental tools. The transgenic non human mammal used for screening (I) for vaccine efficacy.
ADVANTAGE - (I) generates neutralizing ***antibodies*** that effectively neutralize a wide variety of ***primary*** ***isolates*** (especially of ***HIV***).
Dwg.0/12

L23 ANSWER 3 OF 3 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 2000-160579 [14] WPIDS
DNC C2000-050092
TI New antigenic peptide from the CDR2 domain of CD4, for immunization against e.g. human immune deficiency virus.
DC B04
IN WANG, C Y
PA (UNBI-N) UNITED BIOMEDICAL INC
CYC 86
PI WO 9967294 A1 19991229 (200014)* EN 105p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9947048 A 20000110 (200025)
US 6090388 A 20000718 (200037)
ADT WO 9967294 A1 WO 1999-US14030 19990621; AU 9947048 A AU 1999-47048 19990621; US 6090388 A US 1998-100409 19980620
FDT AU 9947048 A Based on WO 9967294
PRAI US 1998-100409 19980620

AB WO 9967294 A UPAB: 20000320
NOVELTY - A CD4-CDR2 antigenic peptide (I) is new.
DETAILED DESCRIPTION - (I) of 30-46 amino acids (aa) contains two Cys

residues separated by a sequence of 28-40 aa that is a contiguous part of residues 27-66 from the 433 aa sequence (all given in the specification) of human CD4 or an immunologically functional homolog of this part.

INDEPENDENT CLAIMS are also included for the following:

(a) synthetic peptides (II) of 50-80 aa containing a helper T cell epitope (Th), (I) and an immunostimulatory invasin domain (Inv);

(b) peptide or peptide conjugate (III) having Th covalently attached to (I);

(c) four specified peptides (IIIa) having Th or Inv attached to (I); and

(d) a composition comprising at least one (III) and a carrier.

ACTIVITY - Antiviral; anti-arthritic; antipsoriatic.

MECHANISM OF ACTION - Induction of polyclonal ***antibodies*** by presentation of neutralizing receptor/co-receptor effector sites. The induced ***antibodies*** block human immune deficiency virus (***HIV***) binding and syncytia formation; they may also block CD4-Class II interactions with other cells; deliver signals to T cells (***inhibiting*** normal CD4+-mediated immunoregulatory functions) or induce apoptosis of CD4 cells by simultaneous engagement of T cell receptors. Polyclonal ***antibodies*** , raised in guinea pigs against the peptide TAKSKKFPSYTATYQFGGFFLLTRILTIPQSLDGGCHWKNWQIKILGNQGSFLTKGPSKLND RADSRRSLWDQGNC (i.e. invasin-GG-T helper epitope-GG-(I)) had 90% neutralizing activity against ***HIV*** of clades A to E at a dilution of 1:20.

USE - Conjugates, or ***fusion*** peptides, containing (I) are used for active immunization to generate ***antibodies*** against CD4 surface complexes, especially to prevent binding of human immune deficiency virus (***HIV***) to CD4 and thus ***HIV*** infection, but also to treat undesirable immune responses such as transplant rejection, or autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus or psoriasis).

ADVANTAGE - Conjugates and peptides containing (I) produce high-titer ***antibodies*** which are broadly neutralizing against ***primary*** ***isolates*** from all clades of ***HIV*** -1 and of ***HIV*** -2. The peptides are cyclically constrained (by a disulfide bridge) and include a promiscuous T helper epitope that is active in genetically diverse subjects.

Dwg.0/0

L24 ANSWER 17 OF 19 AIDSLINE
1993:16557 Document No.: MED-93378778. Synergistic inhibition of HIV-1 envelope-mediated cell fusion by CD4-based molecules in combination with antibodies to gp120 or gp41. ***Allaway G P*** ; Ryder A M; Beaudry G A; Maddon P J. Progenics Pharmaceuticals, Inc., Tarrytown, New York 10591. AIDS RESEARCH AND HUMAN RETROVIRUSES (1993). Vol. 9, No. 7, pp. 581-7. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB CD4-based molecules were tested in combination with HIV-1-neutralizing antibodies directed against the V3 loop of gp120 or against gp41, for inhibition of HIV-1 envelope-mediated cell fusion. A virus-free cell fusion assay was developed, using Chinese hamster ovary cells that stably express HIV-1 gp120/gp41. These cells were incubated with dilutions of CD4-based molecules, antibodies, or mixtures of both, then overlaid with C8166 CD4+ T cells. Syncytia were counted and the degree of inhibition of cell fusion was determined. Synergy, additivity, or antagonism was calculated by the combination index (CI) method. The CD4-based molecules included soluble human CD4 as well as fusion proteins composed of CD4 linked to human immunoglobulin gamma 1 or gamma 2 heavy chains. Combinations of CD4-based molecules and monoclonal or polyclonal anti-V3 loop antibodies were synergistic in blocking HIV-1 envelope-mediated cell fusion (CI = 0.21-0.91 at 95% inhibition). Synergy was also observed with combinations of the CD4-based molecules and a broadly neutralizing anti-gp41 monoclonal antibody (2F5) (CI = 0.29-0.65 at 95% inhibition). These results demonstrate that molecules inhibiting HIV attachment act synergistically with molecules inhibiting HIV-1 fusion. The results suggest that CD4-based therapeutics would be more effective in patients with naturally occurring anti-V3 loop or anti-gp41 antibodies. In addition, there may be an advantage in coadministering CD4-based molecules and antibodies that block fusion, especially broadly neutralizing anti-gp41 antibodies, as a combination therapy for HIV-1 infections.

L24 ANSWER 15 OF 19 AIDSLINE
1996:2119 Document No.: MED-96093887. Expression and characterization of CD4-IgG2, a novel heterotetramer that neutralizes primary HIV type 1 isolates. ***Allaway G P*** ; Davis-Bruno K L; Beaudry G A; Garcia E B; Wong E L; Ryder A M; Hasel K W; Gauduin M C; Koup R A; McDougal J S; et al. Progenics Pharmaceuticals, Inc., Tarrytown, New York 10591, USA. AIDS RESEARCH AND HUMAN RETROVIRUSES (1995). Vol. 11, No. 5, pp. 533-9. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB CD4-IgG2 is a novel fusion protein comprising human IgG2 in which the Fv portions of both heavy and light chains have been replaced by the V1 and V2 domains of human CD4. This tetrameric protein is being developed as an immunoprophylactic agent to reduce the probability of infection following HIV-1 exposure, in settings such as occupational or perinatal exposure to the virus. CD4-IgG2 has been expressed in Chinese hamster ovary cells and is secreted as a fully assembled heterotetramer. The protein binds with nanomolar affinity to purified gp120 from both a laboratory-adapted strain and a primary isolate of HIV-1. Pharmacokinetic studies in rabbits demonstrated that CD4-IgG2 has a plasma terminal half-life greater than 1 day, compared with 15 min for soluble CD4 (sCD4). CD4-IgG2 does not bind to Fc receptors on the surface of U937 monocyte/macrophage cells. Compared to molecules that incorporate the Fc portion of IgG1, CD4-IgG2 has less potential to mediate functions such as antibody-dependent enhancement of infection or transplacental transmission of HIV-1. When tested in a virus-free HIV-1 envelope glycoprotein-mediated cell fusion assay, the tetrameric CD4-IgG2 molecule inhibited syncytium formation more effectively than monomeric sCD4 or a dimeric CD4-gamma 2 fusion protein.

This suggests the protein will block cell-to-cell transmission of HIV-1. Moreover, CD4-IgG2 effectively neutralized a panel of laboratory-adapted strains and primary isolates of HIV-1, including strains with different tropisms and isolated from different stages of the disease, at concentrations that should be readily achieved in vivo.

L24 ANSWER 11 OF 19 AIDSLINE
1996:10164 Document No.: MED-96323171. Human immunodeficiency virus type 1 membrane fusion mediated by a laboratory-adapted strain and a primary isolate analyzed by resonance energy transfer. Litwin V; Nagashima K A; Ryder A M; Chang C H; Carver J M; Olson W C; Alizon M; Hasel K W; Maddon P J; ***Allaway G P*** . Progenics Pharmaceuticals, Inc., Tarrytown, New York 10591, USA. JOURNAL OF VIROLOGY (1996). Vol. 70, No. 9, pp. 6437-41. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Previous studies of human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein-mediated membrane fusion have focused on laboratory-adapted T-lymphotropic strains of the virus. The goal of this study was to characterize membrane fusion mediated by a primary HIV-1 isolate in comparison with a laboratory-adapted strain. To this end, a new fusion assay was developed on the basis of the principle of resonance energy transfer, using HeLa cells stably transfected with gp120/gp41 from the T-lymphotropic isolate HIV-1LA1 or the macrophage-tropic primary isolate HIV-1JR-FL. These cells fused with CD4+ target cell lines with a tropism mirroring that of infection by the two viruses. Of particular note, HeLa cells expressing HIV-1JR-FL gp120/gp41 fused only with PM1 cells, a clonal derivative of HUT 78, and not with other T-cell or macrophage cell lines. These results demonstrate that the envelope glycoproteins of these strains play a major role in mediating viral tropism. Despite significant differences exhibited by HIV-1JR-FL and HIV-1LAI in terms of tropism and sensitivity to neutralization by CD4-based proteins, the present study found that membrane fusion mediated by the envelope glycoproteins of these viruses had remarkably similar properties. In particular, the degree and kinetics of membrane fusion were similar, fusion occurred at neutral pH and was dependent on the presence of divalent cations. Inhibition of HIV-1JR-FL envelope glycoprotein-mediated membrane fusion by soluble CD4 and CD4-IgG2 occurred at concentrations similar to those required to neutralize this virus. Interestingly, higher concentrations of these agents were required to inhibit HIV-1LAI envelope glycoprotein-mediated membrane fusion, in contrast to the greater sensitivity of HIV-1LAI virions to neutralization by soluble CD4 and CD4-IgG2. This finding suggests that the mechanisms of fusion inhibition and neutralization of HIV-1 are distinct.

L33 ANSWER 2 OF 23 AIDSLINE
1999:2640 Document No.: MED-99034616. A new monoclonal ***antibody*** , mAb 4A12, identifies a role for the glycosaminoglycan (GAG) binding domain of RANTES in the antiviral effect against ***HIV*** -1 and intracellular Ca2+ signaling. Burns J M; Gallo R C; DeVico A L; Lewis G K. Divisions of Basic Science and Vaccine Research, Institute of Human Virology, University of Maryland Biotechnology Institute, Baltimore, Maryland 21201, USA. JOURNAL OF EXPERIMENTAL MEDICINE (1998). Vol. 188, No. 10, pp. 1917-27. Journal code: I2V. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The beta-chemokine RANTES (regulated on activation, normal T cell expressed and secreted) suppresses the infection of susceptible host cells by ***macrophage*** ***tropic*** strains of ***HIV*** -1. This effect is attributed to interactions of this chemokine with a 7-transmembrane domain receptor, CCR5, that is required for virus-cell

fusion and entry. Here we identify domains of RANTES that contribute to its biological activities through structure-function studies using a new monoclonal ***antibody*** , mAb 4A12, isolated from mice immunized with recombinant human RANTES. This monoclonal ***antibody*** (mAb) blocked the antiviral activity of RANTES in infectivity assays with ***HIV*** -1Bal, and ***inhibited*** the mobilization of intracellular Ca2+ elicited by RANTES, yet recognized this chemokine bound to cell surfaces. Epitope mapping using limited proteolysis, reversed phase high-performance liquid chromatography, and mass spectrometry suggest that residues 55-66 of RANTES, which include the COOH-terminal alpha-helical region implicated as the glycosaminoglycan (GAG) binding domain, overlap the determinant recognized by mAb 4A12. This is supported by affinity chromatography studies, which showed that RANTES could be eluted specifically by heparin from a mAb 4A12 immunoaffinity matrix. Removal of cell surface GAGs by enzymatic digestion greatly reduced the ability of mAb 4A12 to detect RANTES passively bound on cell surfaces and abrogated the ability of RANTES to elicit an intracellular Ca2+ signal. Taken together, these studies demonstrate that the COOH-terminal alpha-helical region of RANTES plays a key role in GAG-binding, antiviral activity, and intracellular Ca2+ signaling and support a model in which GAGs play a key role in the biological activities of this chemokine.

L33 ANSWER 3 OF 23 AIDSLINE
1999:1758 Document No.: MED-99030883. T-tropic ***human*** ***immunodeficiency*** ***virus*** type 1 (***HIV*** -1)-derived V3 loop peptides directly bind to CXCR-4 and ***inhibit*** T-tropic ***HIV*** -1 infection. Sakaida H; Hori T; Yonezawa A; Sato A; Isaka Y; Yoshie O; Hattori T; Uchiyama T. Laboratory of Virus Immunology, Research Center for Acquired Immunodeficiency Syndrome, Institute for Virus Research, Kyoto University, Kyoto 606, Japan. JOURNAL OF VIROLOGY (1998). Vol. 72, No. 12, pp. 9763-70. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Certain types of chemokine receptors have been identified as coreceptors for ***HIV*** -1 infection. The process of viral entry is initiated by the interaction between an envelope protein gp120 of ***HIV*** -1, CD4, and one of the relevant coreceptors. To understand the precise mechanism of the Env-mediated ***fusion*** and entry of ***HIV*** -1, we examined whether the V3 region of gp120 of T-cell line tropic (T-tropic) virus directly interacts with the coreceptor, CXCR-4, by using five synthetic V3 peptides: two cyclized V3 peptides (V3-BH10 and V3-ELI) which correspond to the V3 regions of the T-tropic ***HIV*** -1 IIIB and ***HIV*** -1 ELI strains, respectively, a linear V3 peptide (CTR36) corresponding to that of ***HIV*** -1 IIIB strain; and cyclized V3 peptides corresponding to that of the ***macrophage*** - ***tropic*** (M-tropic) ***HIV*** -1 ADA strain (V3-ADA) or the dualtropic ***HIV*** -1 89.6 strain (V3-89. 6). FACScan analysis with a CXCR-4(+) human B-cell line, JY, showed that V3-BH10, V3-ELI, and V3-89.6 but not CTR36 or V3-ADA blocked the binding of IVR7, an anti-CXCR-4 monoclonal ***antibody*** (MAb), to CXCR-4 with different magnitudes in a dose-dependent manner, while none of the V3 peptides influenced binding of an anti-CD19 MAb at all. Next, the effects of the V3 peptides on SDF-1beta-induced transient increases in intracellular Ca2+ were investigated. Three V3 peptides (V3-BH10, V3-ELI, and V3-89.6) prevented Ca2+ mobilization. Furthermore, the three peptides ***inhibited*** infection by T-tropic ***HIV*** -1 in a dose-dependent manner as revealed by an MTT assay and a reverse transcriptase assay, while the other peptides had no effects. These results present direct evidence that the V3 loop of gp120 of T-tropic ***HIV*** -1 can interact with its coreceptor CXCR-4 independently of the V1/V2 regions of gp120 or cellular CD4.

L33 ANSWER 10 OF 23 AIDSLINE
1997:21616 Document No.: MED-97404394. ***Antibodies*** to several conformation-dependent epitopes of gp120/gp41 ***inhibit*** CCR-5-dependent cell-to-cell ***fusion*** mediated by the native envelope glycoprotein of a primary ***macrophage*** - ***tropic*** ***HIV*** -1 isolate. Verrier F C; Charneau P; Altmeyer R; Laurent S; Borman A M; Girard M. Departement de Virologie Moleculaire, Institut Pasteur, Paris, France. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA (1997). Vol. 94, No. 17, pp. 9326-31. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The beta-chemokine receptor CCR-5 is essential for the efficient entry of primary ***macrophage*** - ***tropic*** ***HIV*** -1 isolates into CD4(+) target cells. To study CCR-5-dependent cell-to-cell ***fusion*** , we have developed an assay system based on the infection of CD4(+) CCR-5(+) HeLa cells with a Semliki Forest virus recombinant expressing the gp120/gp41 envelope (Env) from a primary clade B' ***HIV*** -1 isolate (BX08), or from a laboratory T cell line-adapted strain (LAI). In this system, gp120/gp41 of the "nonsyncytium-inducing," primary, ***macrophage*** - ***tropic*** ***HIV*** -1BX08 isolate, was at least as fusogenic as that of the "syncytium-inducing" ***HIV*** -1LAI strain. BX08 Env-mediated ***fusion*** was ***inhibited*** by the beta-chemokines RANTES (regulated upon activation, normal T cell expressed and secreted) and macrophage inflammatory proteins 1beta (MIP-1beta) and by ***antibodies*** to CD4, whereas LAI Env-mediated ***fusion*** was insensitive to these beta-chemokines. In contrast soluble CD4 significantly reduced LAI, but not BX08 Env-mediated ***fusion*** , suggesting that the primary isolate Env glycoprotein has a reduced affinity for CD4. The domains in gp120/gp41 involved in the interaction with the CD4 and CCR-5 molecules were probed using monoclonal ***antibodies*** . For the ***antibodies*** tested here, the greatest ***inhibition*** of ***fusion*** was observed with those directed to conformation-dependent, rather than linear epitopes. Efficient ***inhibition*** of ***fusion*** was not restricted to epitopes in any one domain of gp120/gp41. The assay was sufficiently sensitive to distinguish between ***antibody*** - and beta-chemokine-mediated ***fusion*** ***inhibition*** using serum samples from patient BX08, suggesting that the system may be useful for screening human sera for the presence of biologically significant ***antibodies*** .

L33 ANSWER 16 OF 23 AIDSLINE
1997:5990 Document No.: MED-96357076. Cell type-specific ***fusion*** cofactors determine ***human*** ***immunodeficiency*** ***virus*** type 1 tropism for T-cell lines versus primary macrophages. Alkhatib G; Broder C C; Berger E A. Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20892, USA. JOURNAL OF VIROLOGY (1996). Vol. 70, No. 8, pp. 5487-94. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Work in this laboratory previously demonstrated that the tropism of different human immunodeficiency type 1 isolates for infection of human CD4+ continuous cell lines (e.g., T-cell lines and HeLa-CD4 transformants) versus primary macrophages is associated with parallel intrinsic fusogenic specificities of the corresponding envelope glycoproteins (Envs). For T-cell line-tropic isolates, it is well established that the target cell must also contain a human-specific ***fusion*** cofactor(s) whose identity is unknown. In this study, we tested the hypothesis that the Env

fusion specificities underlying T-cell line versus macrophage tropism are determined by distinct cell type-specific ***fusion*** cofactors. We applied a recombinant vaccinia virus-based reporter gene assay for Env-CD4-mediated cell ***fusion*** ; the LAV and Ba-L Envs served as prototypes for T-cell line-tropic and ***macrophage*** - ***tropic*** isolates, respectively. We examined CD4+ promyeloctic and monocytic cell lines that are infectible by T-cell line-tropic isolates and become susceptible to ***macrophage*** - ***tropic*** strains only after treatment with differentiating agents. We observed parallel changes in ***fusion*** specificity: untreated cells supported ***fusion*** by the LAV but not the Ba-L Env, whereas cells treated with differentiating agents acquired ***fusion*** competence for Ba-L. These results suggest that in untreated cells, the block to infection by ***macrophage*** - ***tropic*** isolates is at the level of membrane ***fusion*** ; furthermore, the differential regulation of ***fusion*** permissiveness for the two classes of Envs is consistent with the existence of distinct ***fusion*** cofactors. To test this notion directly, we conducted experiments with transient cell hybrids formed between CD4-expressing nonhuman cells (murine NIH 3T3) and different human cell types. Hybrids formed with HeLa cells supported ***fusion*** by the LAV Env but not by the Ba-L Env, whereas hybrids formed with primary macrophages showed the opposite specificity; hybrids formed between HeLa cells and macrophages supported ***fusion*** by both Envs. These results suggest the existence of cell type-specific ***fusion*** cofactors selective for each type of Env, rather than ***fusion*** ***inhibitors*** for discordant Env-cell combinations. Finally, analyses based on recombinant protein expression and ***antibody*** blocking did not support the proposals by others that the CD44 or CD26 antigens are involved directly in the entry of ***macrophage*** - ***tropic*** isolates.

L35 ANSWER 1 OF 9 AIDSLINE
1999:11546 Document No.: MED-99370192. ***Inhibitory*** mechanism of the CXCR4 antagonist T22 against ***human*** ***immunodeficiency*** ***virus*** type 1 infection. Murakami T; Zhang T Y; Koyanagi Y; Tanaka Y; Kim J; Suzuki Y; Minoguchi S; Tamamura H; Waki M; Matsumoto A; Fujii N; Shida H; Hoxie J A; Peiper S C; Yamamoto N. Department of Microbiology and Molecular Virology, Faculty of Medicine, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo 113-8519, Japan. JOURNAL OF VIROLOGY (1999). Vol. 73, No. 9, pp. 7489-96. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We recently reported that a cationic peptide, T22 ([Tyr(5,12), Lys(7)]-polyphemusin II), specifically ***inhibits*** ***human*** ***immunodeficiency*** ***virus*** type 1 (***HIV*** -1) infection mediated by CXCR4 (T. Murakami et al., J. Exp. Med. 186:1389-1393, 1997). Here we demonstrate that T22 effectively ***inhibits*** replication of T-tropic ***HIV*** -1, including ***primary*** ***isolates*** , but not of non-T-tropic strains. By using a panel of chimeric viruses between T- and M-tropic ***HIV*** -1 strains, viral determinants for T22 susceptibility were mapped to the V3 loop region of gp120. T22 bound to CXCR4 and interfered with stromal-cell-derived factor-1alpha-CXCR4 interactions in a competitive manner. Blocking of anti-CXCR4 monoclonal ***antibodies*** by T22 suggested that the peptide interacts with the N terminus and two of the extracellular loops of CXCR4. Furthermore, the ***inhibition*** of cell-cell ***fusion*** in cells expressing CXCR4/CXCR2 chimeric receptors suggested that determinants for sensitivity of CXCR4 to T22 include the three extracellular loops of the coreceptor.

L35 ANSWER 2 OF 9 AIDSLINE

1998:18810 Document No.: ICA12-98395966. Mechanism(s) of ***HIV*** neutralization by specific ***antibodies*** . Spenlehauer C; Moog C; Kirn A; Aubertin A M. Unite Inserm 74, Institute de Virologie, Strasbourg, France. Int Conf AIDS (1998). Vol. 12, pp. 518 (Abstract No. 31118). Pub. country: Switzerland. Language: English.

AB How do ***antibodies*** neutralize ***HIV*** and ***inhibit*** the productive infection of target cells? Several mechanisms of action have been proposed that include impairment of the binding to the receptor and/or the co-receptor, or interference with post-binding events necessary for the entry of, the virus. Understanding them may provide useful informations to improve vaccinal strategies with aim of inducing efficient neutralizing ***antibodies*** (NAb). In order to examine the steps of the viral cycle affected by NAb, we first studied the kinetic of action of neutralizing sera by adding them at various times before and after the adsorption of the virus on the target cells. The autologous neutralization of ***primary*** ***isolates*** and the neutralization of the T-cell line adapted (TCLA) strain ***HIV*** -1MN were compared. For ***HIV*** -1MN, a preincubation of the virus with the sera was required to achieve neutralization. In contrast, this preincubation was not necessary for ***primary*** ***isolates*** , as the autologous virus could still be neutralized when adding the sera after adsorption on the target cells. Further extensive studies of the steps involved in neutralization, including ***fusion*** and penetration of the virus have been carried out. They highlight differences in the mechanisms of action of NAb according to the virus used, and emphasizes the discrepancy that exists between TCLA strains and ***primary*** ***isolates*** . Indeed, these two types of viruses already contrast by their sensitivity to neutralization and by the involvement of qualitatively different NAb. Altogether our results suggest that TCLA strains are predominantly neutralized through an ***inhibition*** of their binding to the target cell, whereas for ***primary*** ***isolates*** , NAb may also affect post-binding events. By strengthening differences between laboratory and field ***HIV*** -1 isolates, these observations assert the need to further focus studies on ***primary*** ***isolates*** representative of the viruses found in infected individuals.

L35 ANSWER 8 OF 9 AIDSLINE
1995:5888 Document No.: MED-95194731. A broadly neutralizing human monoclonal ***antibody*** against gp41 of ***human*** ***immunodeficiency*** ***virus*** type 1. Purtscher M; Trkola A; Gruber G; Buchacher A; Predl R; Steindl F; Tauer C; Berger R; Barrett N; Jungbauer A; et al. Institute of Applied Microbiology, University of Agriculture, Vienna, Austria. AIDS RESEARCH AND HUMAN RETROVIRUSES (1994). Vol. 10, No. 12, pp. 1651-8. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB We have established a hybridoma clone, designated 2F5, secreting a neutralizing human monoclonal ***antibody*** (MAb) specific for gp41 of ***human*** ***immunodeficiency*** ***virus*** type 1 (***HIV*** -1). The epitope of MAb 2F5 was mapped to amino acid sequence Glu-Leu-Asp-Lys-Trp-Ala on the ectodomain of gp41. In this study different in vitro test systems were used to characterize the neutralizing properties of MAb 2F5. In syncytium ***inhibition*** assays, ***fusion*** ***inhibition*** experiments, and neutralization assays on different ***HIV*** -susceptible cells (H9, U937, and peripheral blood mononuclear cells) MAb 2F5 showed broad-spectrum neutralizing capacity against ***HIV*** -1 laboratory isolates IIIB, MN, RF, and SF2. In addition, ***primary*** ***isolates*** from AIDS patients were also neutralized.

L35 ANSWER 9 OF 9 AIDSLINE
1992:10602 Document No.: MED-92373025. ***Inhibition*** of ***HIV*** infection by a novel CD4 domain 2-specific monoclonal ***antibody*** . Dissecting the basis for its ***inhibitory*** effect on ***HIV*** -induced cell ***fusion*** . Burkly L C; Olson D; Shapiro R; Winkler G; Rosa J J; Thomas D W; Williams C; Chisholm P. Biogen, Inc., Cambridge, MA 02142. JOURNAL OF IMMUNOLOGY (1992). Vol. 149, No. 5, pp. 1779-87. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB ***HIV*** use the CD4 molecule as their primary cellular receptor. Residues in the N-terminal domain (D1) of CD4 are crucial to ***HIV*** attachment through the gp120 envelope component. However, other regions of CD4 appear to be required subsequently for virus- and cell-cell ***fusion*** . Little is understood of the post-binding steps which may differ between ***HIV*** variants. We report a novel anti-CD4 mAb that does not block CD4/gp120 binding, but that does efficiently block both viral infection and cell-cell ***syncytia*** formation, and define its contact site as residues in CD4 D2 using both mouse/human CD4 chimeras and CD4 substitution mutants. We also investigated the basis for its antiviral effect. Using the CD4 D2 specific mAb, we identify another conserved step in ***HIV*** infection, as evidenced by its ability to neutralize a broad range of ***primary*** ***isolates*** and T cell-line passaged strains. Monovalent forms of the mAb were used to determine if its activity was due to masking of the D2 epitope, to steric ***inhibition*** , or bivalency. Our data indicate that both binding site and bivalency of the mAb underlie its potency. The need for bivalency is not simply explained by affinity, because monovalent forms can displace the intact mAb and reverse its protective effect. These results provide evidence that binding of the D2-specific mAb prevents structural alterations necessary for membrane ***fusion*** .

L37 ANSWER 115 OF 194 AIDSLINE
1992:8902 Document No.: MED-92304438. Design, development, and interpretation of ***HIV*** ***neutralization*** assays. Whalley A S; Nguyen M L; Morrow W J. IDEC Pharmaceuticals Corporation, La Jolla, California. VIRAL IMMUNOLOGY (1991). Vol. 4, No. 4, pp. 201-13. Journal code: ADO. ISSN: 0882-8245. Pub. country: United States. Language: English.

AB In developing therapeutic reagents for the control of ***HIV*** infection, it is necessary to screen candidate products in vitro for their ability to reduce or ***neutralize*** viral infection. Although the current literature describes numerous ***neutralization*** assays, no universally accepted standards have been adopted. In this article, we briefly review the available ***neutralization*** assays and describe in detail the methods we have selected in our laboratory for the screening and characterization of reagents with potential anti- ***HIV*** properties. After evaluating many different technical protocols and experimental procedures, we have found the syncytium ***inhibition*** and ***syncytial*** focus assays to be particularly useful and have found p24 gag antigen production to be an excellent objective measure of ***HIV*** infection under a variety of conditions. These assays proved reproducible and sensitive and are suitable for use in the majority of laboratories.

L37 ANSWER 135 OF 194 AIDSLINE
1991:6992 Document No.: MED-91250726. An IgG human monoclonal ***antibody*** that reacts with ***HIV*** -1/GP120, ***inhibits*** virus binding to cells, and ***neutralizes*** infection. Posner M R; Hideshima T; Cannon T; Mukherjee M; Mayer K H; Byrn R A. Department of Medicine, Roger Williams Medical Center, Providence, RI 02908. JOURNAL OF

IMMUNOLOGY (1991). Vol. 146, No. 12, pp. 4325-32. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB A human mAb (HmAb) termed F105 was obtained by ***fusion*** of ***antibody*** -producing EBV-transformed cells with the HMMA2.11TG/O cell line. F105 is an IgG1 kappa ***antibody*** that binds to the surfaces of cells infected with all ***HIV*** -1 strains tested: MN, RF, IIIB, and SF2, but not uninfected cells. The HmAb immunoprecipitates GP120 from all four strains. F105 does not react with denatured GP120 on Western blots, but does react with viral lysates and purified GP120 dotted onto nitrocellulose filter paper under nondenaturing conditions. rGP120 from SF2 and soluble rCD4 ***inhibit*** ***antibody*** binding to infected cells in a dose-dependent manner. F105 ***inhibits*** the binding of free, infectious virions to uninfected HT-H9 cells with 50% of maximal (100%) ***inhibition*** at approximately 1 microgram/ml. F105 ***inhibits*** infection of HT-H9 cells by 100 tissue culture infective dose 50% units of MN and IIIB strains with 50% ***inhibition*** at concentrations of HmAb readily achievable in man. It appears that the F105 HmAb reacts with a conformationally defined epitope on ***HIV*** -1/GP120 that is exposed on the free virion and is important for binding to the cell surface by the virion. The epitope, which is immunogenic in humans, appears to be within, or topographically near, the CD4-binding site. F105 and the F105 epitope are potentially useful in therapy and in the design of peptide or anti-Id based vaccines; monitoring of the expression of the Id may prove useful in evaluating immune responses in infected individuals or vaccinated volunteers.

L37 ANSWER 170 OF 194 AIDSLINE
1990:10522 Document No.: ICA5-00278189. Murine monoclonal ***antibodies*** to a synthetic peptide of ***HIV*** -1 have ***neutralizing*** and ***fusion*** blocking activities. Durda P J; Weinhold K; Matthews T; Rayner M; Bacheler L; Pomerantz R. E.I. du Pont de Nemours and Co., Medical Products Dept., N. Billerica, MA 01862. Int Conf AIDS (1989). Vol. 5, pp. 537 (Abstract No. Th.C.O.26). ISBN: 0-662-56670-X. Pub. country: Canada. Language: English.

AB We have developed a series of murine monoclonal ***antibodies*** (MAbs) to a region of the 120kD envelope glycoprotein of ***HIV*** -1 which has previously been implicated as a site for virus ***neutralization*** . The antigen employed was a synthetic peptide containing 15 amino acids, representing amino acid residues 308-322, RIQRGPGRAFVTIGK, a hypervariable region of env gp120 (HTLV-3B isolate). Five of the MAbs have reactivity with gp120 in Western blots, four of these block ***fusion*** of ***HIV*** -1(3B) infected cells with uninfected cells with one also blocking ***fusion*** of a number of ***HIV*** -1 isolates including MN. At least two show reactivity in immunofluorescence assays with both fixed and live cells, and one has been found to ***neutralize*** ***HIV*** -1(3B) in vitro. These MAbs have been fine mapped using different synthetic peptides and each MAb has been found to have a different reactivity profile. Reactivities with peptides representative of aa's 308-322 of different ***HIV*** -1 strains appear to be predictive of the reactivities of those MAbs with those actual isolates in various biological assays. For example the one MAb which reacts strongly with aa's 308-322 of the MN isolate (both by direct binding in ELISA and in peptide ***inhibition*** of binding of the MAb to aa's 308-322 of 3B) was the only MAb that blocked ***fusion*** of the MN infected cells with uninfected cells and that showed significant binding to MN infected cells as determined by FACS.

L37 ANSWER 93 OF 194 AIDSLINE
1993:6727 Document No.: MED-93221719. Discrete regions of ***HIV*** -1

gp41 defined by ***syncytia*** - ***inhibiting*** affinity-purified human ***antibodies*** . Vanini S; Longhi R; Lazzarin A; Vigo E; Siccardi A G; Viale G. Dipartimento di Biologia e Tecnologia, H. San Raffaele, CNR Istituto di Chimica degli Ormoni, Milan, Italy. AIDS (1993). Vol. 7, No. 2, pp. 167-74. Journal code: AID. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVE: Fine mapping of ***HIV*** -1 gp41 ***fusion*** -critical sites. DESIGN AND METHODS: ***Antibodies*** from human ***HIV*** -1-positive sera were affinity-purified on a panel of synthetic overlapping peptides spanning residues 526-682 of the extracellular portion of ***HIV*** -1 gp41. The syncytium- ***inhibiting*** capacity of the immunopurified ***antibodies*** and their differential reactivity on the synthetic peptides were tested. RESULTS: This approach enabled the identification of residues 583-591 (ARILAVERY), 595-599 (QQLLG), 603-609 (CSGKLIC) and 664-673 (ELLELDKWAS) as possibly involved in the ***fusion*** process. Reduction in the anti-ARILAVERY, anti-CSGKLIC and anti-ELLELDKWAS ***antibody*** titres and frequencies correlates with disease progression. ***Syncytia*** - ***inhibition*** capacity of sera did not correlate with the presence of high-titre ***antibodies*** reacting with any of the peptides tested, suggesting that most ***fusion*** -affecting ***antibodies*** are not directed towards gp41. CONCLUSIONS: This strategy may be relevant for understanding the contribution of anti-gp41 ***antibodies*** in protecting against the pathogenic effects of the virus and in the design of an effective env vaccine.

L39 ANSWER 45 OF 74 AIDSLINE
1996:10164 Document No.: MED-96323171. ***Human*** ***immunodeficiency*** ***virus*** type 1 membrane fusion mediated by a laboratory-adapted strain and a primary isolate analyzed by resonance energy transfer. Litwin V; Nagashima K A; Ryder A M; Chang C H; Carver J M; Olson W C; Alizon M; Hasel K W; Maddon P J; Allaway G P. Progenics Pharmaceuticals, Inc., Tarrytown, New York 10591, USA. JOURNAL OF VIROLOGY (1996). Vol. 70, No. 9, pp. 6437-41. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Previous studies of ***human*** ***immunodeficiency*** ***virus*** type 1 (***HIV*** -1) envelope glycoprotein-mediated membrane fusion have focused on laboratory-adapted T-lymphotropic strains of the virus. The goal of this study was to characterize membrane fusion mediated by a primary ***HIV*** -1 isolate in comparison with a laboratory-adapted strain. To this end, a new fusion assay was developed on the basis of the principle of resonance energy transfer, using HeLa cells stably transfected with gp120/gp41 from the T-lymphotropic isolate ***HIV*** -1LA1 or the ***macrophage*** - ***tropic*** primary isolate ***HIV*** -1JR-FL. These cells fused with CD4+ target cell lines with a tropism mirroring that of infection by the two viruses. Of particular note, HeLa cells expressing ***HIV*** -1JR-FL gp120/gp41 fused only with PM1 cells, a clonal derivative of HUT 78, and not with other T-cell or macrophage cell lines. These results demonstrate that the envelope glycoproteins of these strains play a major role in mediating viral tropism. Despite significant differences exhibited by ***HIV*** -1JR-FL and ***HIV*** -1LAI in terms of tropism and sensitivity to ***neutralization*** by CD4-based proteins, the present study found that membrane fusion mediated by the envelope glycoproteins of these viruses had remarkably similar properties. In particular, the degree and kinetics of membrane fusion were similar, fusion occurred at neutral pH and was dependent on the presence of divalent cations. Inhibition of ***HIV*** -1JR-FL envelope glycoprotein-mediated membrane fusion by soluble CD4 and CD4-IgG2 occurred at concentrations similar to those required to

neutralize this virus. Interestingly, higher concentrations of these agents were required to inhibit ***HIV*** -1LAI envelope glycoprotein-mediated membrane fusion, in contrast to the greater sensitivity of ***HIV*** -1LAI virions to ***neutralization*** by soluble CD4 and CD4-IgG2. This finding suggests that the mechanisms of fusion inhibition and ***neutralization*** of ***HIV*** -1 are distinct.

L39 ANSWER 25 OF 74 AIDSLINE
1998:7581 Document No.: AIDS-98929027. Characterization of highly conserved epitopes in the V(1)/V(2) domain of ***HIV*** -1 gp120 that mediate potent ***neutralization*** of primary ***HIV*** -1 isolates. Pinter A; Burkhart M; Honnen W; Kayman S; Reiken S; Tan G; Trochev O; Wu Z. Public Health Research Institute, New York, NY. Conf Retroviruses Opportunistic Infect (1998). Vol. 5th, pp. 97 (Abstract No. 99). Pub. country: United States. Language: English.

AB The development of an effective vaccine for ***HIV*** -1 is hindered by the genetic and antigenic diversity of the virus and the relative resistance of primary isolates to antibody-mediated ***neutralization*** . We have identified a monoclonal antibody directed against a type-specific epitope in the V(1)/V(2) domain of gp120 that mediates potent ***neutralization*** of both T cell-tropic and ***macrophage*** - ***tropic*** isolates bearing this epitope. In order to generate more broadly crossreactive anti-V1/V(2) antibodies, we immunized rats with a recombinant fusion protein expressing a V(1)/V(2) domain derived from a clinical ***HIV*** -1 isolate containing the clade B V(2) consensus sequence. These animals produced antibodies reactive with heterologous gp 120s and V(1)/V(2) fusion proteins derived from env sequences of multiple clades. V1/V(2)-specific immunoglobulin fractions isolated from sera of immunized animals by affinity chromatography on columns containing immobilized V(1)/V(2) fusion protein possessed potent ***neutralization*** activity for a number of primary ***macrophage*** - ***tropic*** viruses, including isolates from multiple clades. These results indicate that the V(1)/V(2) domain of ***HIV*** -1 gp120 contains epitopes that are broadly conserved across clades, and that some of these epitopes can mediate potent ***neutralization*** of primary viruses. Preliminary characterization of the epitopes involved will be presented and the design of a V(1)/V(2) fusion protein that more effectively presents native epitopes required for elicitation of ***neutralizing*** antibodies will be described.

L39 ANSWER 39 OF 74 AIDSLINE
1997:10380 Document No.: AIDS-97920669. Identification of highly conserved epitopes in the v1/v2 domain of ***HIV*** -1 gp120 that mediate potent ***neutralization*** of ***macrophage*** - ***tropic*** primary isolates. Pinter A; Honnen W J; Wu Z; Troshev O; Kayman S C. Public Health Research Institute, New York, NY. Conf Adv AIDS Vaccine Dev (1996). pp. 38. Pub. country: United States. Language: English.

AB A problem with current ***HIV*** -1 subunit vaccines is their inability to induce antibodies that ***neutralize*** primary, ***macrophage*** - ***tropic*** viral isolates. To study the basis for the relative resistance of ***macrophage*** - ***tropic*** viruses to ***neutralization*** , we examined the ability of monoclonal antibodies against different ***neutralization*** epitopes to ***neutralize*** a matched pair of T cell-tropic and ***macrophage*** - ***tropic*** ***HIV*** -1 molecular clones. Whereas mabs directed against the V3 loop, the CD4-binding domain or a ***neutralizing*** site in gp41 preferentially ***neutralized*** the T cell-tropic isolate, a mab directed against a glycan-dependent epitope in the V2 domain potently

neutralized both T cell-tropic and ***macrophage*** - ***tropic*** isolates. We have identified human sera which contain anti-V1/V2 antibodies with very broad cross reactivities, including cross-clade reactivity, and have found that some of these sera have potent ***neutralizing*** activities for several ***macrophage*** - ***tropic*** ***HIV*** -1 isolates. Depletion of the anti-V1/V2 antibodies by fractionation of these sera on immunoaffinity columns containing immobilized V1/V2 proteins resulted in a significant reduction in the ***macrophage*** - ***tropic*** virus ***neutralization*** titers of these sera. The anti-V1/V2-specific antibodies of one serum were eluted from the column, and were shown to possess potent ***neutralization*** activity for several ***macrophage*** - ***tropic*** isolates. These results demonstrate that the V1/V2 domain is a potent ***neutralization*** target in primary, ***macrophage*** - ***tropic*** viruses, and suggest that vaccines that induce antibodies against the relevant V1/V2 epitopes may provide effective in vivo protection against infection.